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Relationship between uric acid/ albumin ratio and coronary slow flow

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ABSTRACT

Objectives: Although the pathophysiology of coronary slow flow is not fully understood, evidence suggesting endothelial dysfunction and subclinical widespread atherosclerosis in genesis has grown in recent years. Our aim in this study is to investigate the relationship between uric acid/ albumin ratio and coronary slow flow.

Methods: One hundred and five coronary slow flow patients (determined by the Thrombolysis in Myocardial Infarction-frame count method) and one-hundred patients with normal coronary low were included retrospectively. The uric acid/ albumin ratio was investigated in all patients participating.

Results: In the logistic regression analysis, it was revealed that high uric acid levels, uric acid/ albumin ratios, and male gender were independent predictors for coronary slow flow. Among these parameters, the uric acid/ albumin ratio was the best predictor of coronary slow flow. Based on the receiver operating characteristics (ROC) analysis, the cut-off value of uric acid/ albumin ratio ≥ 0.57 was found to predict coronary slow flow with 68.3% sensitivity and 68.7% specificity. In multivariate logistic regression analysis, high uric acid levels (OR: 2.22; 95% CI (1.551-3.200), $p < 0.001$), high serum uric acid/ albumin ratio (OR: 37.7 95% CI (8.176-234.387), $p < 0.001$), male gender (OR: 0.157; 95% CI (0.078-0.318), $p < 0.001$) were independent predictors of coronary slow flow.

Conclusions: High uric acid/ albumin ratio was detected as an independent predictor for coronary slow flow. Larger studies are needed to elucidate its role in the pathophysiology of coronary slow flow.

Keywords: Uric acid, uric acid/ albumin ratio, coronary slow flow

The coronary slow flow was distinguished by a noticeably reduced flow rate of contrast material in one or more coronary arteries during coronary angiography (CAG) despite the absence of coronary stenosis. Although individuals with coronary slow flow are identified as having "normal coronary arteries," it is reasonable to treat coronary slow flow as a separate disease entity. Tambe et colleagues reported "a normal coronary artery tree accompanied with a notably sluggish flow rate of angiographic dye from the main arteries" in individuals with chest discomfort in 1972 [1]. Since then, most studies have characterized coronary slow flow quantitatively by analyzing the Thrombolysis in Myocardial Infarction (TIMI) flow grade or corrected TIMI frame count (CTFC) [2]. The prevalence of coronary slow flow in CAG ranges from 1%

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to 5.5% [3]. Coronary slow flow has been linked to endothelial dysfunction. Endo-myocardial biopsies histological examinations have revealed signs of endothelial dysfunction and microvascular disease in the coronary slow flow scenario [3]. Endothelium-dependent flow-mediated vasodilation has been observed to be decreased in coronary slow- flow patients; however, nitroglycerin-induced endothelium-independent vasodilation was not altered in these people. In addition to arterial endothelial dysfunction, endothelium-dependent vasodilation is also weak in this group. In comparison to persons with normal coronary flow, these patients showed higher plasma levels of asymmetric dimethyl-arginine, endothelin-1, and homocysteine, and lower plasma levels of nitric oxide [4]. Furthermore, a link between microalbuminuria and endothelial dysfunction has been observed in the literature [5]. Albumin, which is a negative acute phase reactant, seems to decrease in this patient group due to renal excretion.

The end product of purine metabolism, serum uric acid, plays a significant role in the genesis and progression of coronary artery disease [6]. When comparing patients with myocardial infarction to healthy persons, the metabolism of amino acids, acyl-carnitines, and purines alters considerably [7]. Many epidemiologic studies have linked hyperuricemia to an increased risk of coronary heart disease, heart failure, and arrhythmias [8]. Elevated serum uric acid indicated the development of coronary artery calcification, and in patients with acute coronary syndrome, elevated serum uric acid was related to higher lipid content of coronary plaque [8]. Furthermore, several variables including age, gender, diet, and medical treatment might alter serum uric acid metabolism. Previous studies have found that having serum uric acid levels above 7 mg/dL increased cardiovascular mortality in patients aged 70 and more [9]. Previous research has found that serum uric acid levels were higher in individuals with systemic hypertension, diabetes, and acute myocardial infarction [10]. Additionally, serum uric acid was associated in earlier research with raised coronary artery calcium, enhanced platelet adhesiveness, and smooth muscle cell proliferation [11]. The fundamental process has not, however, been completely clarified. We evaluated the association between hyperuricemia, the serum uric acid/ albumin ratio, and coronary slow flow in the current study.

METHODS

Study Population

In our clinic, angiography was performed on 1984 patients between July 2019 and December 2022. The coronary slow flow was observed in 130 patients. After exclusion criteria, 105 patients with coronary slow flow who had previously been diagnosed with coronary ischemia by non-invasive methods were consecutively included in this study. 105 patients with slow coronary flow were included in group 1. In the control group, 100 patients were included in group 2. Patients with severe renal failure (creatinine > 2 mg/dL), active infection, acute coronary syndrome or patients with malignancy were excluded from the study. By examining our hospital's database, we were able to determine the fundamental clinical features of the patients. Throughout each patient's hospital stay, fasting blood samples were taken. Automatic equipment was used to measure biochemical values and do whole blood counts on the blood. Blood pressure over 140/90 mmHg or using an antihypertensive drug was considered to be hypertension. Fasting plasma glucose levels of 7.0 mmol/L (126 mg/dL), glycated hemoglobin A1c of 6.5%, or use of antidiabetic medications were considered to be indicators of diabetes mellitus. Being on lipid-lowering treatment or having a total cholesterol level over 220 mg/dL were considered to be symptoms of hyperlipidemia.

The study, which was conducted by the Helsinki Declaration, was approved by the local ethics committee (Date: 23.07.2023, Decision no: 2023.149.07.14).

Coronary Angiography

After receiving informed consent, a standard Judkins technique was used to perform coronary angiography through the right femoral artery with standard projections. Two independent cardiologists who were blinded to the patient information analyzed coronary angiograms. Significant stenosis was defined as 50% or more in at least one major coronary artery. Non-critical coronary artery stenosis was defined as less than 50%. Each patient's coronary frame count was determined using the Gibson *et al*. [12] described TIMI frame count computation. Since the left anterior descending coronary artery (LAD) length caused opacification to take a long time, the TFC value calculated for the LAD was divided by 1.7, and the CTFC was

calculated by multiplying the number of frames obtained for each vessel by 2, taking into account that angiographic recordings were taken in our clinic at a rate of 15 frames per second. The TIMI-3 flow threshold was established at 27 frame numbers. CTFC > 27 was seen as a sign of a malfunction of the microvascular perfusion, and CTFC < 27 was a sign of healthy microvascular perfusion. CTFC values of more than 27 are regarded as diagnostic for coronary slow flow [3].

Statistical Analysis

The statistical program SPSS 22.0 was used to conduct the statistical analysis (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean ± standard deviation (SD) or median (minimum-maximum). Using chi-square or Fischer's exact tests, categorical variables were represented as percentages and compared. The Kolmogorov-Smirnov test was used to assess the normality of data distributions. For contin-

Table 1. Baseline characteristics of the groups

Variable	Group 1 (CSF (+)) (n = 105)	Group 2 (CSF (-)) (n = 100)	Total (n = 205)	*p value*
Age (years)	52 ± 9	50 ± 9	51.5 ± 9.5	0.24
Male	81 (77.1%)	78 (78%)	159 (77.5%)	0.82
Hyperlipidemia	45(42.9%)	35 (39.3%)	80 (41.2%)	0.61
Hypertension	39 (37.1%)	44 (45.8%)	83 (41.3%)	0.21
Smoking	37 (35.2%)	31 (32.3%)	68 (33.1%)	0.35
Diabetes mellitus	27 (25.7%)	35 (36.5%)	62 (30.8%)	0.09
Body mass index (kg/m^2)	27.4 ± 4.04	26.8 ± 4.85	26.4 ± 3.2	0.67
Pharmacological treatment				
Ca–channel blocker	12 (11.4%)	11 (11%)	23 (11.2%)	0.99
ACE-I	30 (28.6%)	24 (25.5%)	54 (27.1%)	0.63
Acetyl salicylic acid	38 (36.2%)	36(36%)	74 (36%)	0.96
Oral antidiabetic	9 (8.5%)	10 (10%)	19 (9.2%)	0.35
Statin	29 (27.6%)	27 (27%)	56 (27.3%)	0.95
Laboratory parameters				
Glucose (mg/dL)	115 ± 25	118.5 ± 30	131.7 ± 86.9	0.07
Creatinin (mg/dL)	0.86 ± 0.15	0.88 ± 0.59	0.87 ± 0.4	0.71
Uric acid (mg/dL)	5.44 (3.4-10.4)	2.28 (1.5-6.7)	2.88 (1-11)	**< 0.001**
Total cholesterol (mg/dL)	188.76 ± 40.2	195.63 ± 44.4	219.1 ± 30.6	0.44
Albumin (g/dL)	4.1 (3-5. 1)	4.9 (3.5-5.2)	4.3 (3-5. 2)	**0.02**
UAR	0.81 (0. 2-2.55)	0.49 (0.25-0.97)	0.67 (0. 2-2.55)	**< 0.001**
Angiographic measurements				
LAD TFC	40.3 ± 9. 9	19.6 ± 5. 8	30.4 ± 13. 2	**< 0.001**
LCX TFC	27.9 ± 6. 9	17.5 ± 4. 5	22.7 ± 8	**< 0.001**
RCA TFC	32.6 ± 9. 4	18.6 ± 6. 8	25.9 ± 10	**< 0.001**

CSF = Coronary slow flow; UAR = uric acid/ albumin ratio, TFC = Corrected TIMI frame count, LAD = Left anterior descending artery, LCX = Left circumflex artery, RCA = Right coronary artery

uously distributed data with a normal distribution, independent samples t-test was applied. The Mann-Whitney U test was used to examine non-normally distributed data. Receiver-operating characteristic analyses (ROC) were utilized to find the serum uric acid/ albumin ratio cut-off values for coronary slow flow prediction. Independent predictors of coronary slow flow were found using multivariate logistic regression analysis. The Spearman correlation test was used to analyze the relationship between the serum uric acid/albumin ratio and the coronary slow flow. Statistics were considered significant for p-values below 0.05.

RESULTS

The baseline characteristics and laboratory results of the patients are summarized in Table 1. The 205 patients' mean age was 51.5 ± 9.5 yrs, and 77.5% of them were male. There was no difference between the two groups in terms of medical treatment and baseline characteristics. The laboratory variables of the two groups were similar except for serum uric acid and the serum uric acid/ albumin ratio, which were higher in group 1 [serum uric acid 5.44 (3.4-10.4) and 2.28 (1.5-6.7), $p < 0.001$; serum uric acid/ albumin ratio 0.81 (0.2-2.55) and 0.49 (0.25-0.97), $p < 0.001$]. The result of the ROC analysis is as follows when the serum uric acid/albumin ratio cut-off value ≥ 0.57 is selected to estimate a coronary slow flow as follows: AUC 0.732; 95% confidence interval (CI) (0.660-0.805) with 68.3% sensitivity and 68.7% specificity (fig. 1). A moderately positive correlation between the serum uric acid/ albumin ratio and coronary slow flow was found using correlation analysis (r = 0.52, $p < 0.001$).

In multivariate logistic regression analysis, high uric acid levels, high serum uric acid/ albumin ratio, male gender were independent predictors of coronary slow flow (uric acid, odds ratio (OR): 2.22; 95% CI (1.551-3.200), $p < 0.001$; serum uric acid /albumin ratio OR: 37.7 95% CI (8.176-234.387), $p < 0.001$, male gender OR: 0.157; 95% CI (0.078-0.318), $p < 0.001$) (Table 2).

DISCUSSION

We investigated the relationship between the coronary slow flow and serum uric acid/ albumin ratio in this study. In our study, high uric acid levels, serum uric acid/ albumin ratio and male gender were independent predictors for coronary slow flow. We found high uric acid levels and serum uric acid/ albumin ratio in the

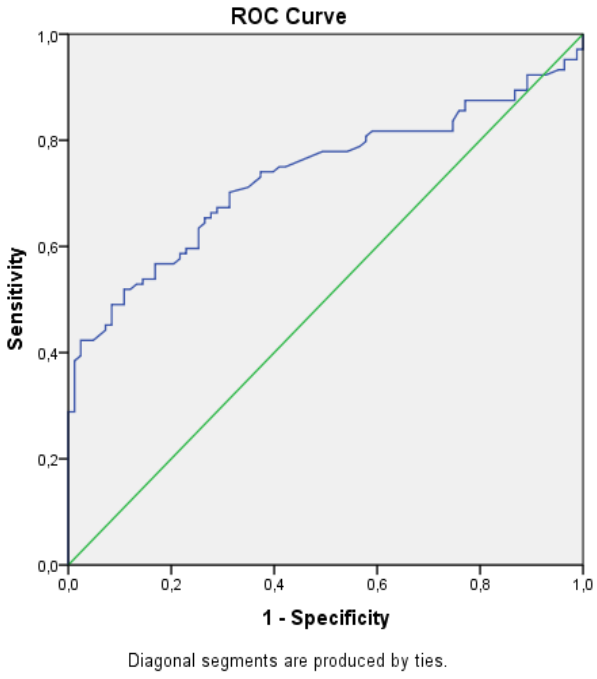

Fig. 1. ROC analysis of uric acid/albumin ratio for predicting coronary slow flow.

Table 2. Univariate and multivariate logistic regression analysis of the independent predictors of coronary slow flow

	Univariate analysis		Multivariate analysis	
Variables	**OR (95% CI)**	***p value***	**OR (95% CI)**	***p value***
UAR	41.4(9.745-176.348)	**< 0.001**	37.7(8.176-234.387)	**< 0.001**
Uric acid	2.451(1.752-3.427)	**< 0.001**	2.22 (1.551-3.200)	**< 0.001**
Age	1.017(0.988-1.048)	0.246	-	-
Gender(male)	0.148(0.079-0.276)	**< 0.001**	0.157(0.078-0.318)	**< 0.001**

UAR = uric acid/ albumin ratio

group with a coronary slow flow.

It has been noted in numerous earlier studies that people aged 70 years and older who have serum uric acid levels above 7 mg/dL have an increased risk of cardiovascular mortality [13]. When present in the acidic/ hydrophobic environment in the cytoplasm of cells or atherosclerotic plaques, serum uric acid transforms into a pro-oxidant substance and increases oxidative stress and through this mechanism, it causes cardiovascular and cerebrovascular diseases [14]. In previous studies, patients with systemic hypertension, diabetes mellitus, and acute myocardial infarction had elevated serum uric acid levels [15]. There was a gradual increase in the risk for acute myocardial infarction, stroke, or CHF over time in the Apolipoprotein MOrtality RISk (AMORIS) and the First National Health and Nutrition Examination Survey (NHANES I) studies [16, 17]. As uric acid permeates cell membranes, inflammation, and oxidation result. Additionally, it decreases the endothelium's production of nitric oxide and prevents cell division and migration. In addition, the expression of proinflammatory cytokines initiates the development of atherosclerosis as well as directly damaging vascular smooth muscle structures. Furthermore, high serum uric acid values and carotid intima-media thickness were found to be significantly correlated in a recent study with 15,843 (73.90% male) participants [18]. In earlier studies, serum uric acid was linked to elevated coronary artery calcium and ectasia, increased smooth muscle cell proliferation, and increased platelet adhesiveness [19]. High serum uric acid levels directly affect vascular smooth muscle, causing endothelial dysfunction and microvascular damage as well as an increase in reactive oxygen species and the activation of the renin-angiotensin system [20]. The underlying mechanism hasn't been fully explained, though. Uric acid is produced in the liver and is primarily eliminated by the kidneys. Kidney damage and cardiovascular disease have both been linked to hyperuricemia, according to studies [21]. An independent predictor of the development of microalbuminuria was baseline serum uric acid, according to a prospective cohort study with 1862 participants who did not have the condition [22]. Hyperuricemia can cause renal injury and microalbuminuria. Based on this, we decided to examine the serum uric acid/albumin ratio in patients with and without coronary slow flow, hoping that microalbuminuria may accompany as well as increased uric acid levels that may cause coronary slow flow. As a matter of fact, in our study, we found high uric acid levels and low albumin levels in the coronary slow flow group, which supports other studies.

Although the epicardial coronary arteries are open in patients with coronary slow flow, they apply to the emergency services due to recurrent chest pain. Although coronary slow flow is relatively benign, it impairs the quality of life. There are also life-threatening arrhythmias such as ventricular tachycardia, myocardial infarction, syncope, and sudden cardiac death in the literature due to coronary slow flow. Although this subgroup's reported mortality is less than 1%, certain individuals may have adverse long-term outcomes, such as myocardial infarction, significant perfusion abnormalities on scintigraphy, or prolonged QT interval on ECG [23]. Additionally, traditional antianginal medication based on guidelines is frequently ineffective for the long-term care of patients with coronary slow flow. Dipyridamole, which affects functional blockage in arteries with sizes under 200µm, was

demonstrated to normalize CTFC, however nitroglycerine, which dilates arteries with diameters more than 200µm, did not. Small coronary arteries under 400 µm have structural and functional abnormalities in the pathogenesis of coronary slow flow. Medial hypertrophy, endothelial swelling, and dysfunction are structural abnormalities, whereas increased resting coronary resistance response to vasodilator is a functional anomaly [24]. We demonstrated that elevated levels of uric acid and serum uric acid /albumin ratio may contribute to the pathogenesis of coronary slow flow in addition to earlier research.

Limitations

The fact that our study was done at a single facility with a small number of patients is its most significant drawback. More blood samples could be obtained from the patients included in our study. Another problem is that some patients were receiving diuretic-based antihypertensive therapy, which could have an impact on their serum uric acid levels. Urinalysis could be performed on patients for microalbuminuria. The results of this study need to be confirmed in larger, multi-center prospective studies.

CONCLUSION

According to our study results; we detected high serum uric acid and low albumin levels in patients with coronary slow flow, and higher serum uric acid/ albumin ratio may predict coronary slow flow.

Authors' Contribution

Study Conception: CA; Study Design: AD; Supervision: CA; Funding: AD; Materials: CA; Data Collection and/or Processing: AD; Statistical Analysis and/or Data Interpretation: CA; Literature Review: AD; Manuscript Preparation: CA and Critical Review: AD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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